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Experimental gene therapy for brain tumors using adenovirus-mediated transfer of cytosine deaminase gene and uracil phosphoribosyltransferase gene with 5-fluorocytosine.

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Transduction of the cytosine deaminase (CD) gene into tumor cells followed by administration of 5-fluorocytosine (5-FC), called 5-FC/CD gene therapy, was created as suicide gene therapy for various cancers. The uracil phosphoribosyltransferase (UPRT) gene, which is absent from mammalian cells, directly converts 5-fluorouracil (5-FU) to 5-fluorouridine 5'-monophosphate. We evaluated whether the coexpression of CD and UPRT genes could generate a synergistic antitumor effect on experimental brain tumors. In vitro study showed that 9L cells, transduced with the UPRT gene by an adenovirus, were 16 times more sensitive to 5-FU, and CD + UPRT-transduced cells were 6,000 times more sensitive to 5-FC than parent cells, indicating that the acquisition of CD and UPRT further increased the 5-FC sensitivity of 9L cells compared with cells transduced with CD alone. In a rat brain tumor model, decreased amounts of CD and UPRT vectors were inoculated into the tumors to detect any additional effect of UPRT. CD and UPRT coexpression followed by 5-FC administration showed an antitumor effect as detected by sequential magnetic resonance imaging. This therapy significantly prolonged animal survival. These results suggest that 5-FC/CD + UPRT gene therapy can enhance the antitumor effect of 5-FC/CD gene therapy. Consequently, this approach might be a more feasible modality for the treatment of malignant brain tumors.

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